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**Published**
*With international search report.*

(54) Title: MANAGEMENT OF PAIN AFTER JOINT SURGERY

(57) Abstract

A method for the management of pain and immobilization resulting from joint surgery comprises administration of an analgetically effective amount of morphine-6-glucuronide (M6G) into the cavity of the joint on which surgery has been performed. Also disclosed is a pharmaceutical composition for use in the method, a single dose of such composition, a hypodermic syringe filled with this single dose, and the manufacture of a medicament for injection into the cavity of a joint on which surgery has been performed, comprising an analgetically effective amount of morphine-6-glucuronide.

No disclosure of M6G.HBr

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# MANAGEMENT OF PAIN AFTER JOINT SURGERY

## FIELD OF THE INVENTION

The present invention relates to a method for the management of pain and immobilization resulting from joint surgery, to composition for use in the method, and to the manufacture of the composition.

## BACKGROUND OF THE INVENTION

Postoperative pain arising after joint surgery, for instance, knee surgery, is often severe and results in long periods of immobilization. The pain is present even at rest and is aggravated during mobilization. It hampers early postoperative mobilization and may prolong hospital care as well as outpatient care. Poor mobilization increases the risk for venous thrombosis and pulmonary embolism. Therefore reduction of pain in patients having undergone joint surgery is of major importance.

At present, patients undergoing knee or other types of orthopedic surgery most often are managed by intravenous or intramuscular morphine or other opoid-based treatments. Usually this results in short-lasting and often insufficient analgesia which may be accompanied by side effects such as nausea, vomiting, and respiratory depression. As an alternative, intravenous or intramuscular NSAIDs (non-steroid anti-inflammatory drugs), such as diclofenac, ketoprofen or ketorolac may be used. Such therapy, however, is not more efficient than administration of opoids while entailing the risk of other side effects such as gastric ulcer, asthma, and severe skin reactions. A better management of postoperative pain thus is desirable.

When given systemically morphine is transformed mainly in the liver to the 3- and 6-glucuronides. The 6-glucuronide (M6G) also is a potent opoid antagonist. It is substantially more hydrophilic than most opoids in clinical use. Therefore M6G has less tendency to penetrate the blood/brain barrier, thus decreasing the risk for adverse central nervous effects.

Morphine 6-glucuronide has been used as a preoperatively intrathecally administered analgesic to reduce postoperative pain in total hip replacement (D Grace et al., Anest. Analg. 83 (1996) 1055-9) and in knee surgery (Brit. J. Anaest. 69 (1992) 2). In both studies the observation of delayed respiratory depression cautions against such use of M6G.

OBJECTS OF THE INVENTION

It is an object of the invention to provide a method for the management of pain and immobilization resulting from joint surgery.

It is another object of the invention to provide a means for the management of pain and immobilization resulting from joint surgery.

Other objects of the invention will become apparent from the following short description of the invention, the description of preferred embodiments thereof, and the appended claims.

SUMMARY OF THE INVENTION

According to the invention is provided a method of the aforementioned kind, comprising the administration of a analgetically effective amount of morphine-6-glucuronide (M6G) into the cavity of the joint on which surgery has been performed.

Since local opoid analgesia may have a slow onset of action due to the gradual upregulation of the opoid receptors during the immediate post operative period, administration of M6G is advantageously combined with that of a local anesthetic with a short onset of action, such as lidocaine, bupivacaine, mepivacaine, and ropivacaine, providing anesthesia of medium or long duration, such as up to 3 h and longer. While the local anesthetic will exert an immediate but shorter lasting effect, the onset of action of M6G will be slower but its effect will be substantially longer than that of the local anesthetic. In combination the local anesthetic and M6G thus will exert a beneficial analgesic effect covering an extended period of time from administration and up to 48 hour or more. This long lasting analgesic effect will let the patient be mobilized earlier, and thus reduce the risk of adverse effects related to postoperative immobilization, such as venous thrombosis and pulmonary embolism. Early mobilization also translates to reduced health care costs.

An advantageous aspect of the invention is that only a fraction of M6G is needed to obtain an analgetic effect (measured at a given point in time post surgery) comparable to that obtained with morphine. In the systemic circulation the concentration of M6G will be very low; it might be even below the detection threshold. This translates to

substantially reduced central nervous effects - as well as adverse effects - which may not be even noticeable. A preferred dose for obtaining analgesia in a larger joint is from 0.05 to 10 mg. In the context of this application 'larger joint' refers to such as the knee joint, the hip joint, the shoulder joint, the elbow joint, and the ankle joint. Preferred doses for the local anesthetic with short onset vary according to its nature. For bupivacain and mepivacaine a dose of 5 mg to 100 mg is preferred.

Another advantageous aspect of the invention is the longer duration of analgesic effect obtained with M6G. This may be due to the hydrophilicity of M6G by which it is retained for a longer time in the synovial fluid of the joint to which it had been administrated. This retention also translates a substantially reduced risk for adverse central nervous effects.

Administration of M6G or of M6G in combination with a short acting local anesthetic will be into the joint capsule, either at the end of surgery before closing the capsule or upon completion of surgery.

According to still another advantageous aspect of the invention the method according to the invention comprises the administration of a non-steroid anti-inflammatory drug (NSAID), such as diclofenac, ketorolac, ketoprofen, ibuprofen, naproxen, indometacin, celecoxib and their pharmacutically acceptable salts or another nonselective NSAID (COX1/COX2) or COX2 selective drug.

According to the invention is also disclosed a pharmaceutical composition for administration to a joint comprising an amount of morphine-6-glucuronide (M6G)

effective for producing postoperative analgesia in the joint and a pharmaceutically acceptable carrier. In particular the analgesically effective amount of M6G is selected to provide an analgesic effect of at least 24 hrs, more preferred at least 48 hrs. It is also preferred for the composition to comprise a short-acting local anesthetic with a short onset of action, such as lidocaine, bupivacaine, mepivacaine, and ropivacaine and their pharmaceutically acceptable salts, but of comparatively short duration, such as a duration of up to one hour or up to three hours.

The pharmaceutically acceptable carrier may be simply saline but also other carriers are conceivable, such as an aqueous solution of hyaluronic acid which is a substitute for synnovial fluid. Thereby an extension of the duration of analgesia may be obtained.

In addition to its application in the context of joint surgery the composition of the invention has further uses, such as in treating articular inflammation.

In the following the invention will be described in more detail by reference to a preferred but not limiting embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

**Example 1**

Immediately upon meniscectomy (three patients; m, 35 y; m, 18 y; m, 20 y) 0.5 mg M6G and 25 mg of bupivacaine hydrochloride in 2 ml saline were injected into the articular space. The patients were mobilized for the first time already the next day, and could leave the hospital on

the 2nd day post surgery. They did not complain of any side effects, and remained substantially free of pain until being dismissed. At the same hospital patients receiving traditional intra-articular analgesia (morphine, 10 mg; bupivacaine, 25 mg) are usually dismissed on the third day after surgery, and often even later. Many of them experience adverse effects caused by morphine, such as nausea and vomiting.

**Example 2**

A composition of the invention for in form of a single dose intra-articular administration in connection with surgery of a larger joint was prepared by dissolving a multiple of 0.5 mg of morphine-6-glucuronide (Pharmacopeia Nordica) and 25 mg of bupivacaine hydrochloride in 2 ml of saline and filling hypodermic syringes under sterile conditions therewith. The composition is ready for use.

**Example 3**

A composition of the invention similar to that of Example 2, but providing extended duration of effect, was prepared by exchanging the saline for an aqueous solution of sodium hyaluronate (Sinvisc™ Roche, containing 8 mg sodium hyaluronate, 8.5 mg sodium chloride, 0.17 mg disodium hydrogen phosphate, and 0.03 mg sodium dihydrogen phosphate per ml).

# Claims

1. A method for the management of pain and immobilization resulting from joint surgery, comprising administration of an analgetically effective amount of morphine-6-glucuronide (M6G) into the cavity of the joint on which surgery has been performed.

2. The method of claim 1, comprising administration of an analgetically effective amount of a local anesthetic with a short onset of action.

3. The method of claim 2, wherein the local anesthetic is selected from the group consisting of lidocaine, bupivacaine, mepivacaine, ropivacaine including its pharmaceutically acceptable salts.

4. The method of any of claims 1 to 3, wherein the effective amount of M6G is from 0.05 mg to 10 mg for a larger joint.

5. The method of any of claims 2 or 3, wherein the effective amount of the local anesthetic is from 1 mg to 100 mg.

6. The method of any of claims 1-5, comprising the administration of pharmacologically effective amount of a non-steroid anti-inflammatory drug (NSAID) into the cavity of the joint or systemically.

7. The method of claim 6, wherein the NSAID is selected from the group consisting of diclofenac, ketorolac, ketoprofen, ibuprofen, naproxen, indometacin, celecoxib including its pharmaceutically acceptable salts.

8. A pharmaceutical composition for injection into the cavity of a joint on which surgery has been performed, for the management of pain and immobilization resulting from joint surgery, comprising an analgetically effective amount of morphine-6-glucuronide (M6G) and a pharmaceutically acceptable carrier.

9. The composition of claim 8, wherein the amount of M6G is from 0.05 mg to 10 mg.

10. The composition of claim 8 or 9, comprising an analgetically effective amount of a local anesthetic with a short onset of action.

11. The composition of claim 10, wherein the local anesthetic is selected from the group consisting of lidocaine, bupivacaine, mepivacaine, ropivacaine including its pharmaceutically acceptable salts.

12. The composition of any of claims 8 - 11, comprising a non-steroid anti-inflammatory drug (NSAID).

13. The composition of claim 12, wherein the NSAID is selected from the group consisting of diclofenac, ketorolac, ketoprofen, ibuprofen, naproxen, indometacin, celecoxib including its pharmaceutically acceptable salts.

14. The composition of any of claims 8 - 13, comprising means for retention of M6G in the joint cavity.

15. The composition of claim 14, wherein said means is hyaluronic acid or a pharmaceutically acceptable salt thereof.

16. A single dose of a pain-relieving composition for intra-articular administration comprising from 0.05 mg to 10 mg of morphine-6-glucuronide and a pharmaceutically acceptable carrier.

17. The single dose of claim 16, comprising from 1 to 100 mg of a member of the group consisting of lidocaine, bupivacaine, mepivacaine, ropivacaine and their pharmaceutically acceptable salts.

18. A hypodermic syringe filled with the single dose of claim 16 or 17.

19. The manufacture of a medicament for injection into the cavity of a joint on which surgery has been performed, comprising an analgetically effective amount of morphine-6-glucuronide (M6G).

20. The manufacture of claim 19, wherein the amount of M6G is from 0.1 mg to 10 mg.

21. The manufacture of claim 19 or 20, wherein the medicament comprises an analgetically effective amount of a local anesthetic with a short onset of action.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00620

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/7042, A61P 23/02, A61P 29/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | Anesth Analg, Volume 83, 1996, Grace,D. et al, "A Comparison of Intrathecal Morphine-6-Glucuronide and Intrathecal Morphine Sulfate as Analgesics for Total Hip Replacement" page 1055 - page 9 -- | 1-21 |
| X | The Annals of Pharmacotherapy, Volume 29, February 1995, Thompson, Dennis, F. et al, "Local Analgesia with Opioid Drugs" page 189 - page 190 -- | 1-21 |
| X | Brittish journal of anaesthesia, Volume 69, No 2, 1992, A.J. COE et al, "INTRATHECAL MORPHINE-6-GLUCURONIDE AND BUPIVACAINE FOR POSTOPERATIVE PAIN" page 221P -- | 1-21 |

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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|---|---|
| 26 July 2000 | 01 -08- 2000 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Eva Johansson/gh<br>Telephone No. +46 8 782 25 00 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00620

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | UK 2282758 A (EUROCELTIQUE S.A.), 19 April 1995 (19.04.95) -- | 1-21 |
| A | WO 9303051 A1 (SALFORD ULTRAFINE CHEMICALS AND RESEARCH LIMITED), 18 February 1993 (18.02.93) -- | 1-21 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00620

**Box I** **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-7
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

**Box II** **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00620

Claims 1-7 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| UK 2282758 A | 19/04/95 | NONE | |
| WO 9303051 A1 | 18/02/93 | AT 173269 T | 15/11/98 |
| | | AU 672365 B | 03/10/96 |
| | | AU 2389492 A | 02/03/93 |
| | | CA 2114838 A | 18/02/93 |
| | | DE 69227588 D | 00/00/00 |
| | | EP 0597915 A,B | 25/05/94 |
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| | | ES 2130175 T | 01/07/99 |
| | | FI 940534 A | 05/04/94 |
| | | GR 3029369 T | 28/05/99 |
| | | HU 68169 A | 29/05/95 |
| | | HU 9400330 D | 00/00/00 |
| | | JP 7501317 T | 09/02/95 |
| | | NO 940349 A | 16/03/94 |
| | | US 5621087 A | 15/04/97 |
| | | US 5977326 A | 02/11/99 |